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AN 2000264937 MEDLINE

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TI Invasive examination of cardiovascular disease.

AU Horimoto M; Takenaka T; Igarashi K; Inoue H; Akino M

CS Division of Cardiology, Sapporo National Hospital.

SO RINSHO BYORI. JAPANESE JOURNAL OF CLINICAL PATHOLOGY, (2000 Feb) 48 (2)  
128-37. Ref: 28

Journal code: KIV. ISSN: 0047-1860.

CY Japan

DT Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW LITERATURE)

LA Japanese

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AN 1999242350 MEDLINE

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TI Short-term and long-term effects of low-density lipoprotein (LDL) apheresis on restenosis after percutaneous transluminal coronary angioplasty (PTCA): is lowering Lp(a) by LDL apheresis effective on restenosis after PTCA?

AU Kanemitsu S; Takekoshi N; Matsui S; Tsugawa H; Ohkubo S; Kitayama M; Matsuda T; Senma J; Masuyama K; Yamagata T; Murakami E

CS Department of Cardiology, Kanazawa Medical University, Kahoku-gun, Ishikawa-ken, Japan.

SO Ther Apher, (1998 Feb) 2 (1) 65-70.

Journal code: DBB. ISSN: 1091-6660.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199907

EW 19990703

N6

L10 ANSWER 6 OF 41 MEDLINE

AN 1999240278 MEDLINE

DN 99240278

TI Clinical application and effectiveness of low-density lipoprotein apheresis in the treatment of coronary artery disease.

AU Daida H; Yamaguchi H

CS Department of Cardiology, Juntendo University School of Medicine, Tokyo, Japan.

SO Ther Apher, (1997 Aug) 1 (3) 253-4.

Journal code: DBB. ISSN: 1091-6660.

CY United States

DT (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

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## Short-Term and Long-Term Effects of Low-Density Lipoprotein (LDL) Apheresis on Restenosis after Percutaneous Transluminal Coronary Angioplasty (PTCA): Is Lowering Lp(a) by LDL Apheresis Effective on Restenosis after PTCA?

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**Abstract:** It has been reported that serum lipoprotein(a) (Lp[a]) levels in patients with restenosis after percutaneous transluminal coronary angioplasty (PTCA) were significantly higher than in patients without restenosis. In this study, we evaluated the preventive effect of LDL apheresis on restenosis after PTCA in patients with hypercholesterolemia. For 10 patients who had shown a serum cholesterol level of more than 220 mg/dl despite treatment with antihypercholesterolemic drugs, LDL apheresis was conducted every 2 weeks after a successful PTCA until restenosis could be checked. In 4 patients, LDL apheresis was conducted for 2 years. LDL apheresis significantly reduced serum cholesterol from  $248 \pm 22$  mg/dl to  $135 \pm 26$

mg/dl and Lp(a) from  $42 \pm 34$  mg/dl to  $21 \pm 16$  mg/dl. The average degree of stenosis in the 11 lesions undergoing PTCA was  $92 \pm 6\%$  before PTCA,  $35 \pm 10\%$  immediately after PTCA, and  $38 \pm 19\%$  at 3 to 4 months after PTCA. Restenosis was observed in only 1 lesion. In 4 patients who received LDL apheresis for 2 years, restenosis did not occur in any of the 4 lesions treated. We concluded that LDL apheresis was an efficacious therapy to prevent restenosis after PTCA in patients with hypercholesterolemia. **Key Words:** Restenosis after percutaneous transluminal coronary angioplasty—Lipoprotein(a)—Low-density lipoprotein apheresis.

Percutaneous transluminal coronary angioplasty (PTCA) has been shown to be effective in relieving myocardial ischemia in patients with coronary artery disease. Restenosis after PTCA occurs in approximately 25 to 40% of patients (1-5), but there are no established preventive measures against restenosis. Restenosis after PTCA cannot be successfully prevented by any drugs including heparin (6), antiplatelet drugs (7), anticoagulants (8), calcium channel blockers (9), thromboxane A<sup>2</sup> receptor blockers (10), and steroids (11). Recently, lipoprotein(a) (Lp[a]) has attracted attention as an independent

risk factor in coronary disease (12) and is an indicator of myocardial infarction (13), unstable angina (14), and vein graft stenosis after a bypass procedure (15). It is reported that Lp(a) is elevated in patients with restenosis after PTCA (16,17). In this study, we evaluated the usefulness of low-density lipoprotein (LDL) apheresis in reducing serum cholesterol and Lp(a) levels to prevent restenosis after PTCA in patients with hypercholesterolemia.

### METHOD

#### Study population

The study population consisted of 10 patients, 1 with acute myocardial infarction, 5 with previous myocardial infarction, and 4 with effort angina pectoris. Eligibility criteria for this study included a se-

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rum cholesterol level of 220 mg/dl or more despite treatment with 2 or 3 types of antihypercholesterolemic drugs among pravastatin, probucol, and cholestyramine, and successful PTCA. The angioplasty procedure was performed by the femoral approach according to standard technique. PTCA was considered successful if it reduced the diameter of the stenosis to 50% or less. We performed 9 elective PTCA and 1 emergency PTCA.

### Study design

Ten patients who underwent successful PTCA procedures were enrolled in this study. All patients, treated with antihypercholesterolemic drugs, underwent LDL apheresis every 2 weeks after a successful PTCA for 3 to 4 months until restenosis could be confirmed. Thereafter 4 patients underwent LDL apheresis for 2 years. The first LDL apheresis session was performed 2 to 3 days after PTCA, and an average of 3 L of plasma was processed in each procedure to reduce serum cholesterol. LDL apheresis was performed with the selective plasma LDL adsorption method using a membrane plasma separator, the Sulflux FS-OS, and dextran sulfate cellulose columns, the Liposorber LA-40 columns (Kaneka Corporation, Osaka, Japan) (18). Blood access was obtained by puncturing the bilateral peripheral veins with an angiocutter. The processing volume of each LDL apheresis session was determined by the serum cholesterol level of each patient. Follow-up coronary arteriograms were performed 3–4 months after PTCA. In 4 patients who underwent LDL apheresis for 2 years, follow-up coronary arteriograms were performed 2 years after PTCA. We measured coronary stenosis using computer analysis (Catex CCIP-310), and measurements were made in a single projection, showing the most severe stenosis. We defined restenosis as narrowing of over 50% of the patency obtained by PTCA.

### Serum lipid measurements

In all patients, blood samples were drawn after a 12 h fast the morning after admission. All patients had been treated with 2 or 3 types of drugs, consisting of pravastatin, probucol, and cholestyramine, but their serum cholesterol levels were higher than 220 mg/dl. We measured the levels of total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, apolipoprotein (apo) A-I, apo B, and Lp(a) before and after LDL apheresis in all patients. The levels of total cholesterol and triglyceride were determined (19) with intraassay. The HDL cholesterol levels were determined enzymatically using the same method as that used for total

cholesterol. Values for the LDL cholesterol levels were calculated using the Friedewald formula (20). Apo A-I and apo B levels were determined by radioimmunoassay (21). Lp(a) was measured using a commercially available enzyme linked immunosorbent assay (ELISA) kit (Tint Eliza Lp[a] kit, Biopool AB, Umea, Sweden) (22). The assay, which uses polyclonal antibodies raised against purified Lp(a), has been shown to be specific, sensitive, reproducible, and appropriate for routine clinical application.

### Statistical analysis

Changes in serum lipids attributable to LDL apheresis were compared using the unpaired Student's *t*-test. Changes in coronary stenosis before and after PTCA were compared using the unpaired *t*-test. Probability levels of less than 0.05 were considered to be significant. Data are expressed as means  $\pm$  SD.

## RESULTS

### Characteristics of study patients

Ten patients who underwent successful PTCA participated in the study (Table 1). They were 9 men and 1 woman, aged from 50 to 62 years, with an average age of  $54 \pm 7$  years. One patient had acute myocardial infarction, 5 patients had previous myocardial infarction, and 4 patients had angina pectoris. PTCA was performed in 10 patients on 11 lesions, including 4 left anterior descending artery (LAD), 6 left circumflex artery (LCX), and 1 right coronary artery (RCA). The balloon sizes used were three 2.5 mm, seven 3.0 mm, and one 3.5 mm. The reference diameter was  $3.23 \pm 0.75$  mm, the minimum diameter was  $0.25 \pm 0.19$  mm, and the percent diameter stenosis was  $92 \pm 6\%$  before PTCA. Clinical success without major complication was achieved in all patients, but 2 patients had minor dissection at the PTCA sites. All patients were treated with 2 or 3 types of drugs, including pravastatin, probucol, and cholestyramine, but their serum cholesterol levels remained higher than 220 mg/dl.

### Changes in serum lipids before and after LDL apheresis

LDL apheresis treatment significantly decreased the levels of serum cholesterol, triglyceride, LDL cholesterol, apo B, and Lp(a), but there was no change in the level of HDL cholesterol (Table 2). Serum cholesterol significantly decreased from  $248 \pm 22$  to  $135 \pm 26$  mg/dl, LDL cholesterol from  $184 \pm 33$  to  $86 \pm 23$  mg/dl, apo B from  $125 \pm 14$  to  $67 \pm 12$

TABLE 1. Patients' baseline characteristics

Patient	Age (years)	Sex	Diagnosis	PTCA performed vessel	Serum cholesterol (mg/dl)	Triglyceride (mg/dl)
KK	50	M	Previous MI	LCX	406	166
KM	62	M	Previous MI	LCX	270	168
NT	60	M	AP	RCA	377	63
JM	62	M	AP	LAD	255	181
NS	62	F	AP	LCX	232	635
MN	49	M	Acute MI	LAD	320	103
TN	44	M	AP	LCX	236	127
MH	52	M	Previous MI	LAD	262	165
MH	50	M	Previous MI	LCX	247	160
MS	45	M	Previous MI	LAD	268	318

PTCA, percutaneous transluminal coronary angioplasty; M, male; F, female; MI, myocardial infarction; LCX, left circumflex artery; RCA, right coronary artery; LAD, left anterior descending artery; AP, angina pectoris.

mg/dl, and Lp(a) from  $42 \pm 34$  to  $21 \pm 16$  mg/dl (Fig. 1). However, in about 2 weeks, serum cholesterol and Lp(a) returned to their pretreatment levels.

#### Changes in coronary stenosis

The average degree of stenosis in the 11 lesions undergoing PTCA was  $92 \pm 6\%$  before PTCA,  $35 \pm 10\%$  immediately after PTCA, and  $38 \pm 19\%$  at 3–4 months after PTCA (Table 3). Restenosis was observed in 1 lesion 3–4 months after PTCA. Ten lesions did not show restenosis. The incidence of restenosis in the patients was 10% and for lesions was 9% in the hypercholesterolemic patients undergoing LDL apheresis. Four patients underwent LDL apheresis for 2 years, and restenosis did not occur in any of their 4 lesions. The average degree of stenosis in the 4 lesions was  $38 \pm 5\%$  (Table 4).

#### A patient who developed restenosis after PTCA despite LDL apheresis

A 49-year-old hypercholesterolemic man with severe chest pain was admitted to our hospital 5 h after the onset of chest pain. Emergency coronary angiography revealed that his LCX segment 13 had 98% stenosis with delayed filling, so we performed direct PTCA on this lesion. PTCA successfully dilated the segment up to 47%. This patient was hypercholesterolemic and had been treated with pravastatin and probucol at a nearby hospital, but his serum cholesterol was 320 mg/dl, and Lp(a) was 80 mg/dl on admission to our hospital. He had acute myocardial infarction, and an LDL apheresis session was performed 6 days after hospitalization. After LDL apheresis was carried out with a plasma processing volume of 3 L, his cholesterol decreased from  $276 \pm$

TABLE 2. Changes in serum lipids before and after LDL apheresis

Patient	Cholesterol (mg/dl)		Triglyceride (mg/dl)		HDL-cholesterol (mg/dl)		LDL-cholesterol (mg/dl)		Apo(b) (mg/dl)		Lp(a) (mg/dl)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
KK	282	158	86	47	25	26	235	123	152	84	39	21
KM	228	135	255	105	39	39	181	75	108	65	21	9
NT	233	101	67	23	36	34	184	62	146	66	25	10
JM	249	138	110	35	29	28	198	103	117	76	26	14
NS	220	90	237	63	30	31	131	46	116	43	31	13
MH	283	117	142	31	23	26	225	83	130	52	114	41
TN	240	123	106	26	33	29	181	88	123	59	8	4
MH	230	146	284	133	26	29	133	84	115	72	9	6
MH	247	160	118	37	29	30	189	121	112	73	93	55
MS	267	179	195	74	40	34	178	70	130	77	53	36
Mean $\pm$ SD	248 $\pm$ 22	135 $\pm$ 28	160 $\pm$ 77	57 $\pm$ 37	31 $\pm$ 6	31 $\pm$ 4	184 $\pm$ 33	86 $\pm$ 25	125 $\pm$ 15	67 $\pm$ 12	42 $\pm$ 35	21 $\pm$ 17

LDL, low-density lipoprotein; HDL, high-density lipoprotein; Apo(b), apolipoprotein (b); Lp(a), lipoprotein (a); SD, standard deviation.

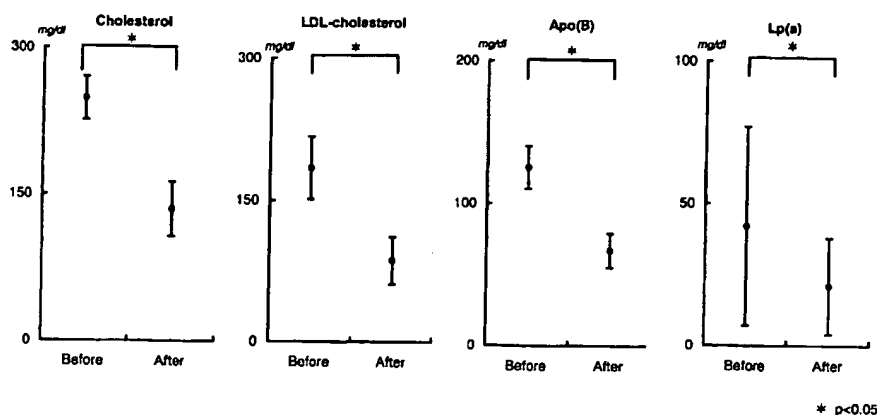


FIG. 1. As shown by the changes in serum lipids before and after LDL apheresis, serum cholesterol, LDL cholesterol, apo B, and Lp(a) are significantly decreased by LDL apheresis.

24 to  $119 \pm 31$  mg/dl and Lp(a) from  $94 \pm 28$  to  $53 \pm 25$  mg/dl (Fig. 2). Coronary angiography performed 1 month later revealed that the PTCA site of his LCX segment 13 had no restenosis. LDL apheresis was repeated once every 2 weeks on an outpatient basis, but the Lp(a) level after 4 months remained at 100 mg/dl. Coronary angiography after 4 months revealed that the PTCA site segment 13 had 87% stenosis, indicating the development of restenosis.

### DISCUSSION

Restenosis after successful PTCA remains a major problem. The results of several clinical trials using anticoagulants, calcium antagonists, corticosteroids, or mechanical interventions have failed to show any effect on the restenosis rate. Recently Lp(a) has attracted attention as an independent risk factor for atherosclerotic coronary disease. In addition, because apo A specific to Lp(a) is similar in structure to plasminogen, Lp(a) competitively suppresses the binding between the plasminogen activator and plasminogen (23). From the viewpoint of the relation-

ship between Lp(a) and the blood coagulation-fibrinolytic system, attention has focused on Lp(a) as a risk factor for atherosclerosis. Previous reports have established that elevated Lp(a) is a predictor of myocardial infarction, angiographic coronary artery disease, and vein graft stenosis after bypass procedures. James reported that serum Lp(a) levels in patients with restenosis after PTCA were significantly higher than in patients without restenosis, and serum Lp(a) levels were a potent predictor of restenosis after PTCA. In our study, we performed LDL apheresis to prevent restenosis in patients with hypercholesterolemia and investigated the therapeutic effect of aggressively reducing serum cholesterol and Lp(a). LDL apheresis sessions were repeated once every 2 weeks for 3 to 4 months in all 10 patients, and serum cholesterol significantly decreased from  $244 \pm 27$  to  $135 \pm 26$  mg/dl and Lp(a) from  $42 \pm 34$  to  $21 \pm 16$  mg/dl. The incidence of restenosis for the patients was 10% and for the lesions was 9%. Four patients who underwent LDL apheresis for 2 years did not experience restenosis in any of their four lesions. In a patient who developed restenosis after PTCA, se-

TABLE 3. Changes in coronary stenosis before PTCA, immediately after PTCA, and 3-4 months after PTCA

Patient	PTCA vessel	Before PTCA (%)	Immediately after (%)	After 3-4 months (%)	Restenosis (%)
KK	LCX	95	39	37	-
KM	LCX	84	15	20	-
NT	RCA	97	37	34	-
JM	LAD	89	35	50	-
	LCX	96	27	34	-
NS	LAD	92	24	42	-
MH	LCX	98	47	87	+
TN	LAD	98	40	28	-
MH	LCX	95	30	20	-
MH	LCX	87	46	35	-
MS	LAD	81	44	25	-
Mean $\pm$ SD		$92 \pm 6$	$35 \pm 10$	$38 \pm 19$	

PTCA, percutaneous transluminal coronary angioplasty; LCX, left circumflex artery; RCA, right coronary artery; LAD, left anterior descending artery; SD, standard deviation.

TABLE 4. Changes in coronary stenosis

Patient	PTCA vessel	Before PTCA (%)	Immediately after (%)	After 3-4 months (%)	After 2 years (%)
KK	LCX	91	41	31	45
KM	LCX	82	41	32	36
NS	LAD	82	33	30	37
MH	LCX	89	34	22	34
	Mean $\pm$ SD	86 $\pm$ 5	37 $\pm$ 4	29 $\pm$ 5	38 $\pm$ 5

PTCA, percutaneous transluminal coronary angioplasty; LCX, left circumflex artery; RCA, right coronary artery; LAD, left anterior descending artery; SD, standard deviation.

rum Lp(a) levels remained very high despite the LDL apheresis. This study suggested that LDL apheresis was an efficacious therapy to prevent restenosis after PTCA and that Lp(a) might influence the development of restenosis after PTCA. Evidence from a post-PTCA autopsy series and angiography in patients has shown that mural thrombus formation is present in the majority of patients (24). Thrombus is thought to provide growth promoting or chemotactic factors including platelet derived growth factor, thrombin, and serotonin (25). Because Lp(a) interferes with fibrinolysis through inhibition of binding between plasminogen and plasminogen activator, Lp(a) may influence the formation of thrombus after PTCA. Another possibility is that Lp(a) or its derivatives promote growth of vascular smooth muscle cells. However, there are no known studies examining this possibility, and our study is too small to evaluate this possibility. Hypercholesterolemia is an important risk factor for coronary atherosclerosis, but its role in coronary restenosis remains unclear. Myler et al. (26), in a report on 494 patients, described a history of hypercholesterolemia in the 6 months preceding PTCA as a significant risk factor for restenosis after PTCA. Reports concerning the effect of lipid lowering drugs on the prevention of restenosis after PTCA have been widely discordant. Rakesh observed that lovastatin significantly reduced the incidence of restenosis after successful PTCA with possible mechanisms being decreases in

serum cholesterol level and smooth muscle cell proliferation (27). Okamura et al. (28) reported that in 6 familial hypercholesterolemic patients who received PTCA under LDL apheresis, no restenosis was observed. Their results are similar to ours. LDL apheresis can be safely performed without any side effects except for hypotension, which may occur at the beginning of treatment in some patients but can be easily improved with the infusion of saline. However, serum cholesterol and Lp(a) nearly return to pretreatment levels after 2 weeks, and it is necessary to conduct LDL apheresis at least every 2 weeks.

In conclusion, LDL apheresis treatment significantly reduced serum lipids, and it was an efficacious therapy in the prevention of restenosis after PTCA in patients with hypercholesterolemia.

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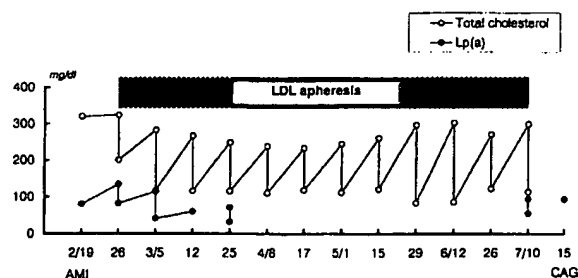


FIG. 2. Shown are the changes in serum cholesterol and Lp(a) before and after LDL apheresis (open circle, total cholesterol; closed circle, Lp(a)).

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